REMARKS

Claims 27, 29-30, 33-40, 42-54, 59-67, 73-75, 84-85 and 90-104 are pending in the application. In the Office Action mailed August 4, 2005, claims 27, 29-30, 33-40, 42-54, 59-67, 73-75, 84-85 and 90-104 are rejected.

Consideration of the following remarks is respectfully requested.

THE REJECTIONS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 27, 29-30, 33-40, 42-54, 59-67, 73-75, 84-85 and 90-104 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,900,659 ("Lo") in view of Lockhart et al., Nature Biotechnology 14:1675-1680 ("Lockhart"). In the Office Action mailed August 4, 2005, the Examiner acknowledges that Lo does not teach evaluating probes having a predetermined base sequence. However, the Examiner contends that Lockhart teaches a method for evaluating a polynucleotide probe having a predetermined base sequence. The Examiner contends that it would have been obvious to a person skilled in the art to apply known sequence analysis for probe selection as taught by Lockhart to the probe selection method of Lo for the expected benefit of obtaining useful probes based on sequence information. Applicant respectfully disagrees with the Examiner for the reasons presented below.

1. SUMMARY OF THE INVENTION

The presently claimed invention relates to a method for evaluating a binding property of a polynucleotide probe comprising a predetermined nucleotide base sequence to a target nucleotide sequence (see the instant specification at page 3, line 35 through page 4, line 3 and page 5, lines 22-32). The method comprises determining a ratio of the amount of hybridization of polynucleotides in a first sample to the polynucleotide probe and the amount of hybridization of polynucleotides in a second sample to the polynucleotide probe (see page 40, line 30, through page 41, line 36; and page 48, line 28, through page 49, line 11). The ratio is used as a measure of the binding property (see page 40, line 30, through page 41, line 36). The first sample is a "specific" hybridization sample in which a substantial portion of the polynucleotide molecules are polynucleotide molecules comprising the target nucleotide sequence (*e.g.*, at least 75% pure of polynucleotide molecules comprising the target

nucleotide sequence), whereas the second sample is a "non-specific" hybridization sample which comprises a plurality of different polynucleotide molecules having different polynucleotide sequences (see, e.g., the instant specification at page 6, line 13, through page 7, line 17 and page 7, lines 27-33).

The first sample can be a sample which is at least 75% pure, at least 90% pure, at least 95% pure, or at least 99% pure in polynucleotide molecules comprising the target nucleotide sequence (see, e.g., the instant specification at page 6, lines 33-37).

The second sample can be a sample comprising nucleotide sequences of a plurality of genes or gene transcripts of a cell or organism (see, e.g., the instant specification at page 6, lines 23-30 and page 7, lines 2-5). The second sample can also be a sample that does not comprise the target sequence, i.e., each different polynucleotide molecule in the second sample does not comprise the target nucleotide sequence, e.g., a polynucleotide sample from a deletion mutant of the cell or organism, where the deletion mutant of the cell or organism does not express the target gene or gene transcript (see, e.g., the instant specification at page 6, lines 23-30 and page 7, lines 2-5 and lines 11-17). The second sample can also be a sample that comprises the target sequence as well as other non-target sequences, e.g., a polynucleotide sample from a wild-type strain of the cell or organism, wherein the wild-type strain of the cell or organism expresses the target gene or gene transcript (see, e.g., the instant specification at page 7, lines 11-17).

In specific embodiments of the claimed invention, the first sample further comprises polynucleotide molecules that do not comprise the target nucleotide sequence, and the second sample comprises: (a) polynucleotide molecules comprising the target nucleotide sequence, and (b) a plurality of different polynucleotide molecules, each different polynucleotide molecule comprising a different nucleotide sequence and not comprising the target nucleotide sequence (see, e.g., the instant specification at page 9, line 17 through page 10, line 5; and page 33, lines 20-25). In one embodiment, the amount of polynucleotide molecules in the first sample comprising the target nucleotide sequence differs from the amount of polynucleotide molecules in the second sample comprising the target nucleotide sequence by at least a factor of two, at least a factor of four, at least a factor of eight, at least a factor of twenty, or at least a factor of 100 (see, e.g., the instant specification at page 33, lines 28-21). In another embodiment, each polynucleotide molecule that does not comprise the target

nucleotide sequence in the first sample is present in the second sample in an amount that differs from the amount of said polynucleotide molecule in the first sample by no more than a factor of 100, no more than a factor of 10, no more than 50% (see, e.g., the instant specification at page 34, lines 2-6). In still another embodiment, the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules that do not comprise the target nucleotide sequence in the plurality of different polynucleotide molecules of the second sample by no more than a factor of two, no more than 50%, no more than 10%, no more than 1% (see, e.g., the instant specification at page 34, lines 12-15).

The invention also relates to a method for evaluating a binding property of a plurality of polynucleotide probes having predetermined nucleotide base sequence to a target nucleotide sequence (see, e.g., the instant specification at page 10, lines 7-9). The method comprises determining a ratio of the amount of hybridization of polynucleotides in a first sample to each polynucleotide probe in the plurality of polynucleotide probes and the amount of hybridization of polynucleotides in a second sample to each polynucleotide probe in the plurality of polynucleotide probes. The first and second samples can be those described above in connection with the method for evaluating a binding property of a probe (see, e.g., the instant specification at page 10, lines 9-15).

2. THE REFERENCES

Lo teaches a method for identifying, among different probes having unknown sequences, those that exhibit specificity to *N. gonorrhoeae* but not to *N. meningitidis*, wherein the genomic sequences of neither strain are taught by Lo. The probes of Lo are fragments from *N. gonorrhoeae* chromosomal DNA. In Lo, *N. gonorrhoeae* chromosomal DNA is digested into fragments (see, Lo, col. 5, Section A). Each of the fragments is inserted into a vector to form a recombinant molecule (see, Lo, col. 6, Section B). The recombinant molecule is transformed into a suitable host, e.g., *E. coli* (Lo, col. 6, Sections C and D). The recombinant molecules are amplified (Lo, col. 7, Section E). The recombinant molecules are then screened against *N. gonorrhoeae* and *N. meningitidis* chromosomal DNAs to identified those sequences that are specific for *N. gonorrhoeae* (Lo, col. 8, Section F). The screening is carried out using test dots each consisting of denatured purified chromosomal DNA from either *N. gonorrhoeae* or *N. meningitidis*, i.e., each test dot consists of

chromosomal DNA from one strain of *N. gonorrhoeae* or *N. meningitidis* (Lo, col. 8, lines 13-19). A recombinant molecule is identified if the ratio of its hybridization amount to a test dot containing fragments of chromosomal DNA of a strain of *N. gonorrhoeae* and its hybridization amount to a test dot containing fragments of chromosomal DNA of a strain of *N. meningitidis* is greater than a preset value, e.g., 5 (Lo, col. 10, lines 55-67). Thus, Lo teaches a method of identifying probes that exhibit a ratio of hybridization to a test dot containing fragments of chromosomal DNA of a strain of *N. gonorrhoeae* and hybridization to a test dot containing fragments of chromosomal DNA of a strain of *N. meningitidis* without knowledge of the sequence of the probes.

Lockhart teaches methods for expression monitoring using high density DNA microarrays. In Lockhart, a method is disclosed for selecting probes based on the sequence features of the probes. The method involves hybridizing respectively pools of specific cytokine RNAs and complex RNA populations that did not contain the cytokine RNAs to the 16,000 probe murine cytokine arrays. Data obtained from these experiments were used to extract a set of heuristic rules by a direct analysis of probe behavior as a function of certain sequence features or to train a neural network model (Lockhart, page 1680, left column). The 16,000 probe arrays contain for each target RNA a set of probe pairs, each probe pair containing a perfect-match probe (PM) and a mismatch probe (MM) (Lockhart, page 1676, right column). The abundance of a target RNA is determined based on the difference between the signals of a PM probe and a corresponding MM probe (Lockhart, page 1679, right column). Thus, Lockhart teaches selecting of probes according to the difference in binding properties of a PM and a MM, not according to a ratio between the amount of a probe's hybridization to the pool of specific cytokine RNAs and the amount of probe's hybridization to the complex RNA population that did not contain the cytokine RNAs.

3. ARGUMENTS

A finding of obviousness under 35 U.S.C. §103 requires a determination of: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the difference between the claimed subject matter and the prior art; and (4) whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1 (1966).

The relevant inquiry is: (1) whether the prior art suggests the invention; and (2)

whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

When selective combination of prior art references is required to render obvious a subsequent invention, "[i]t is insufficient that the prior art disclosed the components of the patented device, either separately or used in other combinations; there must be some teaching, suggestion, or incentive to make the combination made by the inventor." *Northern Telecom, Inc. v. Datapoint Corp.* 908 F2d. 931, 934 (Fed. Cir. 1990) "[T]here must be some reason for the combination other than the hindsight gleaned from the invention itself. There must be 'something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination." *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985).

The case law has been especially vigorous on guarding against using "hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." See, e.g., *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). The Federal Circuit said in *In re Dembiczak*

> Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is *rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references*. ... Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight.

In re Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1999) (emphasis added). With respect to what might meet the requirement of a showing of motivation, the Federal Circuit said that

> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, *the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.*

In re Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998) (emphasis added). The Examiner must "explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination." *In re Rouffet*, 149 F.3d

1350, 1357 (Fed. Cir. 1998) (emphasis added). With respect to the sources where motivation to combine may be found, the Federal Circuit stated that "[t]his court has identified three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998)

The case law further held that each reference must be evaluated as a whole, i.e., disclosures in the reference that diverge from and teach away from the invention can not be disregarded. "Not only must the claimed invention as a whole be evaluated, but so also must the references as a whole, so that their teachings are applied in the context of their significance to a technician at the time--a technician without our knowledge of the solution." *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985). "It is *impermissible* within the framework of a Section 103 rejection *to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the reference fairly suggests* to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965) (emphasis added).

In the present instance, the relevant inquiry is whether the prior art suggests combining Lo, which teaches a method for identifying probes that exhibit a certain ratio of hybridization of the probe to *N. gonorrhoeae* and hybridization of the probe to *N. meningitides*, without using sequence information, with Lockhart, which teaches a sequence based probe selection method for selecting a pair of PM and MM probes, the signal difference between which provides a measure of abundance of a RNA target, such that the rejected claims would be rendered obvious.

Applicant respectfully submits that Lo in combination with Lockhart does not render the rejected claims obvious, and that one skilled in the art would not have been motivated to combine the teachings of Lo with Lockhart in a manner so as to render the rejected claims obvious.

Firstly, Applicant respectfully submits that, as discussed above and acknowledged by the Examiner, Lo does not teach or suggest a method for evaluating a binding property of a polynucleotide probe having a predetermined nucleotide base sequence. The purpose of Lo's method is to identify probes without knowledge of the sequences. This is demonstrated

clearly by Lo's method itself: (i) purification and digestion of *N. gonorrhoeae* chromosomal DNA; (ii) formation of a recombinant molecule; (iii) transformation of the recombinant molecule into a suitable host; (iv) screening of host cells; (v) amplification of the recombinant molecule; (vi) hybridizing each recombinant molecule to test dot consisting of denatured purified chromosomal DNA from a single strain of either *N. gonorrhoeae* or *N. meningitides*; (vii) determining a ratio of hybridization amount to a test dot containing fragments of chromosomal DNA of a strain of *N. gonorrhoeae* and its hybridization amount to a test dot containing fragments of chromosomal DNA of a strain of *N. meningitidis*; and (viii) identifying those recombinant molecules having a ratio greater than a preset value (see also Lo, at col. 5, lines 1-14, for a summary of its method steps). Lo does not teach or suggest using sequence information or determining the sequence of its target and/or probes. Nor does Lo teach or suggest the desirability of using or determining the sequences of its target and/or probes. Instead, its method steps are chosen such that probes can be obtained from the chromosomal DNA of *N. gonorrhoeae* without knowledge of either the target sequence or the probe sequences. A person skilled in the art would understand that such a method is not for evaluating binding properties of probes having known sequences. A person skilled in the art would not be motivated to use sequence information in Lo's method.

Lockhart teaches a method of selecting pairs of PM and MM probes having predetermined sequences for measuring the abundances of RNA targets. Lockhart teaches extracting heuristic rules or a neural network model from hybridization data of the 16,000 probe murine cytokine array to a pool of specific cytokine RNAs and to a complex RNA population that did not contain the cytokine RNAs. Lockhart does not teach or suggest comparing directly a probe's hybridization amount to the pool of specific cytokine RNAs with the probe's hybridization amount to the complex RNA population, much less combining the two hybridization amounts of a probe into a single quantity, e.g., a ratio, and using such a single quantity as a measure of the binding property of the probe. Lockhart does not teach or suggest using probe sequence information in evaluating such a single quantity measure of binding property. Nor does Lockhart teach or suggest any advantage or desirability of utilizing sequence information in evaluating such a single quantity measure of binding property of a probe. Thus, Lockhart does not supplement what are missing in Lo, and neither cited reference provides motivation for the combination.

Applicant next respectfully submits that the combination as contended by the Examiner is clearly a result of "hindsight reconstruction by picking and choosing among isolated disclosures in the prior art to deprecate the claimed invention." Using the inventor's disclosure as a blueprint, the Examiner picks and chooses only selective teachings from Lo and Lockhart to defeat the claimed invention. In particular, the Examiner picks from Lo the teachings of hybridizing each recombinant molecule to a test dot consisting of denatured purified chromosomal DNA from a single strain of either *N. gonorrhoeae* or *N. meningitides*, and determining a ratio of the amount of hybridization of the recombinant molecule to a test dot containing fragments of chromosomal DNA of a strain of *N. gonorrhoeae* and the amount of hybridization of the recombinant molecule to a test dot containing fragments of chromosomal DNA of a strain of *N. meningitidis*, i.e., Lo's steps (vii) and (viii) discussed above, and from Lockhart the teaching of evaluating probes that have known sequences to support the obviousness rejection. The Examiner does not provide evidence why a person skilled in the art would have picked such selective teachings from Lo and Lockhart. Applicant respectfully submits that the Examiner does not evaluate each reference as a whole because the Examiner disregards disclosures in the references that diverge from the invention.

The case law is clear that in order to guard against using "hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention," the Examiner must "explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination." In the Office Action, in an attempt to show motivation to combine the selected teachings from Lo and Lockhart, the Examiner first contends that "Lockhart et al further teach their method of probe selection, based on sequence information, 'provides a way to use directly the growing body of sequence information for highly parallel experimental investigation .... Simultaneous monitoring of tens of thousands of genes.'" (see, Office Action, page 4, lines 2-5) Applicant respectfully points out that, as discussed above, when considered as a whole, a person skilled in the art would understand that Lockhart teaches a method of selecting pairs of PM and MM probes for determining the signal differences of PMs and MMs. Lockhart does not teach or suggest comparing directly a probe's hybridization amount to the pool of specific cytokine RNAs with the probe's hybridization amount to the complex RNA population, much less combining the two hybridization amounts of a probe into a single quantity, e.g., a ratio, and using such a single

quantity as a measure of the binding property of the probe. Thus, Lockhart's teaching provides at most suggestion of using sequence information in selecting probes for use in a scheme that utilizes perfect-match and mismatch probe pairs, and does not provide suggestion of using sequence information in Lo's method.

The Examiner also contends that "it would have been obvious to one of ordinary skill in the art ... to apply known sequence analysis for probe selection as taught by Lockhart et al to the probe selection method of Lo et al for the expected benefit of obtaining useful probes based on the growing body of sequence information ...." Applicant respectfully points out that a vague, non-specific assertion of achieving "the expected benefit of obtaining useful probes based on the growing body of sequence information" is not adequate as evidence of motivation and suggestion. As discussed above, Lo's method is designed to identify probes without using sequence information. The Examiner does not provide evidence regarding how the "known sequence analysis" for selecting perfect-match and mismatch probe pairs taught by Lockhart may be applied to the probe selection method of Lo. The Examiner does not provide evidence regarding how sequence information may benefit Lo's method. For example, the Examiner does not provide evidence regarding what particular benefit Lo's method is expected to receive by using sequence information. The Examiner does not provide evidence regarding which sequence or sequences are useful. In this regard, Lo used 6 strains of *N. gonorrhoeae* and 6 strains of *N. meningitides*, and screened 3000 probes (see, Lo, col. 13, lines 13-20). The Examiner does not provide evidence regarding which sequences of the genomic sequence(s) of which strain or strains of *N. gonorrhoeae* or *N. meningitides* and/or the sequences of the screened probes should be used. The Examiner does not provide evidence regarding where or how to obtain any such sequences. Thus, the Examiner's contention is nothing more than "[b]road conclusory statements regarding the teaching of multiple references," which, standing alone, "are not 'evidence.'" *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999).

The Examiner also fails to evaluate each reference as a whole. As discussed above, the Examiner chooses Lo's teachings of hybridizing each recombinant molecule to test dot consisting of denatured purified chromosomal DNA from a single strain of either *N. gonorrhoeae* or *N. meningitides*, and determining a ratio of the amount of hybridization of the recombinant molecule to a test dot containing fragments of chromosomal DNA of a strain of *N. gonorrhoeae* and the amount of hybridization of the recombinant molecule to a test dot

containing fragments of chromosomal DNA of a strain of *N. meningitidis*, i.e., Lo's steps (vii) and (viii) discussed above, but disregards Lo's method steps that do not use or rely on sequence information, i.e., Lo's steps (i)-(vi). On the other hand, the Examiner chooses Lockhart's teaching of evaluating probes that have known sequences, but disregards the parts of Lockhart's method that teaches selecting pairs of PM and MM probes for determining the signal differences between PM probes and MM probes. Applicant respectfully submits that when Lo is evaluated as a whole, it will be clear to a person skilled in the art that Lo does not teach or suggest using sequence information in its method, whereas when Lockhart is evaluated as a whole, it will be clear to a person skilled in the art that Lockhart does not teach using sequence information in deriving a single quantity measure of a binding property of the probe. In *In re Wesslau*, the court has held that "[i]t is *impermissible* within the framework of a Section 103 rejection *to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the reference fairly suggests* to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965) (emphasis added).

Applicant further respectfully points out that the Examiner also characterizes various teachings of Lo incorrectly. For example, the Examiner contends that Lo teaches a first sample which comprises a plurality of molecules comprising the target chromosomal DNA from a strain of *N. gonorrhoeae*. Applicant respectfully submits that such a contention is true only if the "plurality of molecules" are intact chromosomal DNA molecules of *N. gonorrhoeae*, because each of the molecule would then comprise the entire chromosomal DNA. Lo does not teach such a sample. To the contrary, Lo teaches shearing chromosomal DNAs in preparing its test dots (see, e.g., Lo, col. 22, lines 11-15). The Examiner also contends that Lo teaches a second sample which comprises chromosomal DNA from a plurality of different strains of *N. gonorrhoeae* and *N. meningitidis*, i.e., a second sample comprising "chromosomal DNA from *N. gonorrhoeae*, strains 53415, 53416, 53417, 53418 and 53419 and chromosomal DNA from *N. gonorrhoeae*, 53420, 53421, 53422, 53423, 53424, 53425" (see, Office Action at page 3). As discussed above, Lo teaches that each individual test dot, i.e., each sample, consists of DNA molecules from one strain of either *N. gonorrhoeae* or *N. meningitidis*. Lo does not teach a test dot that comprises a mixture of chromosomal DNA from two or more different strains. Lo teaches using hybridization to each individual dot in the screening of the recombinant molecules. Thus, Lo teaches neither a first sample which comprises a plurality of molecules comprising the target chromosomal

DNA from a strain of *N. gonorrhoeae* nor a second sample comprising "chromosomal DNA from *N. gonorrhoeae*, strains 53415, 53416, 53417, 53418 and 53419 and chromosomal DNA from *N. gonorrhoeae*, 53420, 53421, 53422, 53423, 53424, 53425."

Therefore, Applicant respectfully submit that Lo in view of Lockhart does not render claims 27, 67, 91 and 93 obvious.

With respect to the dependent claims, Applicant respectfully submits that because independent claims 27, 67, 91 and 93 are not rendered obvious by Lo in view of Lockhart, the dependent claims are also nonobvious. The Federal Circuit has held that "[d]ependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious." *In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988). Applicant respectfully submits that Lo and Lockhart, alone or in combination, do not render claims 27, 29-30, 33-40, 42-54, 59-67, 73-75, 84-85 and 90-104 obvious, and the rejection of these claims under 35 U.S.C. § 103(a) based on Lo in view of Lockhart should be withdrawn.

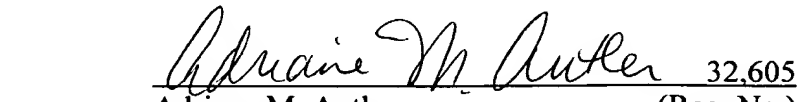
CONCLUSION

Applicant respectfully requests entry of the foregoing remarks into the file of the above-identified application. Applicant believes that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application are respectfully requested.

No fee is believed due in connection with this Response. However, should the Patent and Trademark Office determine otherwise, please charge the required fee to Jones Day Deposit Account No. 50-3013. A copy of this sheet is enclosed.

Respectfully submitted,

Date: November 3, 2005



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Express Mail No EV654850687US
Date Mailed: 11/3/2005
Serial No. 09/616,849 Filed July 14, 2000
Inventor Burchard
For METHOD FOR DETERMINING THE SPECIFICITY AND SENSITIVITY OF OLIGONUCLEOTIDES FOR HYBRIDIZATION

The stamp of the Patent Office hereon may be taken as an acknowledgment of the date stamped of the following:

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File no.: 9301-044 Sender: AMA/WW